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THE PHYSICAL-ORGANIC CHEMISTRY OF SURFACES,
AND ITS RELEVANCE TO MOLECULAR RECOGNITION

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19. ABSTRACT (Continue on reverse if necessary and identify by block number) Understanding the interactions between liquids and the surfaces of organic solids is important for the study of molecular recognition. One method for studying these interactions is based on a physical organic approach: formation of well characterized organic surfaces and comparison of the contact angles of liquids on these surfaces. The technique of self-assembly provides an excellent route for the syntheses of organic surfaces; alkanethiols, for example, self-assemble from solutions to form monolayers on gold. Properties of these monolayers, including their thickness and their wettability by water, can be controlled by manipulating the structure and functionality of the molecules used to form the monolayer. The wettability of monolayers on gold formed from $\text{HS}(\text{CH}_2)_n\text{CH}_3$ or					
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19. Abstract (Continued)

$\text{HS}(\text{CH}_2)_{11}\text{O}(\text{CH}_2)_n\text{CH}_3$, where n is the number of methylene groups, depends only on the composition the outermost 5-10 Å angstroms of the monolayer. The wettability of monolayers formed from mixtures of $\text{HS}(\text{CH}_2)_{11}\text{CH}_3$ and $\text{HS}(\text{CH}_2)_{21}\text{CH}_3$ depends both on the structure of the outermost part of the monolayer and the structure of the liquid. These and other results suggest that this physical-organic approach has and will continue to provide valuable insight into molecular recognition.

Keywords: Biocompatibility, Proteins, Liquids, Biochemistry

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THE PHYSICAL-ORGANIC CHEMISTRY OF SURFACES, AND ITS
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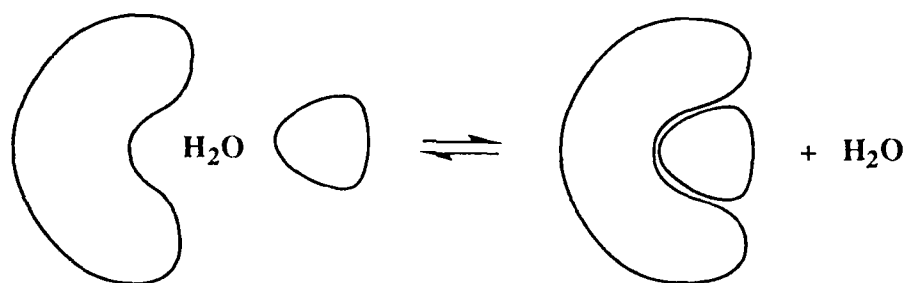
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Molecular recognition in most biological systems is the result of summing large numbers of small, compensating energies between the parts of the interacting components. In biological systems, there are, as a rule, three major interacting components -- a protein (a receptor or enzyme), a ligand (the molecular being recognized), and water (Figure 1). Other participating molecules -- ions, membranes, small organic molecules, additional ligands -- may be important in some circumstances, but can, as a first approximation, be neglected.

How should one think about the interactions between these three major participants? Protein-water and ligand-water interactions should be easier to understand than protein-ligand interactions, since water is a homogeneous medium (or at least more homogeneous than protein or ligand). Even for interactions involving water, however, the intuition of the chemist or biochemist is less than perfect. In principle, and in due course, all will be calculated by the computer, and advances in molecular mechanics and molecular dynamics have been rapid in the last years.¹ The fact remains, however, that at the present time most of the success in practical applications of molecular recognition -- especially to drug design and molecular pharmacology -- has been based on the time-honored patterns of classical medicinal chemistry.

We have been interested in a problem whose relevance to molecular recognition apparently lies at the farthest boundaries of the subject -- that is, the physical-organic chemistry of wetting. Our interest is to understand how fluids, especially water, interact with



van der Waals
 H-Bond
 Electrostatic
 Water
 Conformational Change
 $\Delta G = \Delta H - T\Delta S$

Figure 1. A schematic illustration of the interaction between a protein and a ligand in water.

solids or immiscible liquids.² In brief, what molecular interactions determine the energies of interfaces -- liquid-solid, solid-vapor, and liquid-vapor? These configurations are relevant to molecular recognition and receptor-ligand binding, because the same interactions determine wetting and recognition. In wetting, however, the systems are structurally very simple -- in principle no more than one molecularly homogeneous, smooth liquid interacting with an equally homogeneous, smooth surface (of a solid or liquid). In molecular recognition, by contrast, the interacting components are rough (on a molecular scale) and heterogeneous. Nonetheless, by understanding the interaction of a large, homogeneous, model surface with water, we should be able to help to understand the interaction of a small patch of protein having similar physical characteristics with water. By examining a number of surfaces modelling different parts of the protein, we may be able to contribute to understanding the global interactions of a protein (or a ligand) with water, and, ultimately, of a protein with a ligand. Conversely, if we cannot understand the interaction of homogeneous surfaces with pure water, our ability to understand the much more complex interactions occurring in biological systems will remain unsatisfactory at any level deeper than empirical modelling.

In order to study solid-liquid interactions using the approaches of physical-organic chemistry, we must be able to prepare surfaces having well-defined structures, to vary the structures of these surfaces, and to measure one or more properties of the system that give information about the energetics of the interfaces of interest. Our work has been addressed primarily to two subjects -- development of methods for the preparation of structurally well-defined organic surfaces using a group of techniques called collectively "molecular self-assembly," and the inference of liquid-solid interactions through the measurement of contact angles.^{3,4}

Self-Assembled Monolayers. The principles of self-assembly are well illustrated by the best developed and most thoroughly investigated of the systems that form organic monolayers -- long-chain alkylthiols $\text{HS}(\text{CH}_2)_n\text{X}$ adsorbed on gold. In this technique, one exposes a clean gold film to a solution or vapor of an organic thiol (Figure 2).⁵ The sulfur atoms of the thiol coordinate to the gold and are converted (by presently undefined mechanisms) to gold thiolates having a geometry determined by the local coordination chemistry of the sulfur and gold. The alkyl chains arrange themselves to minimize

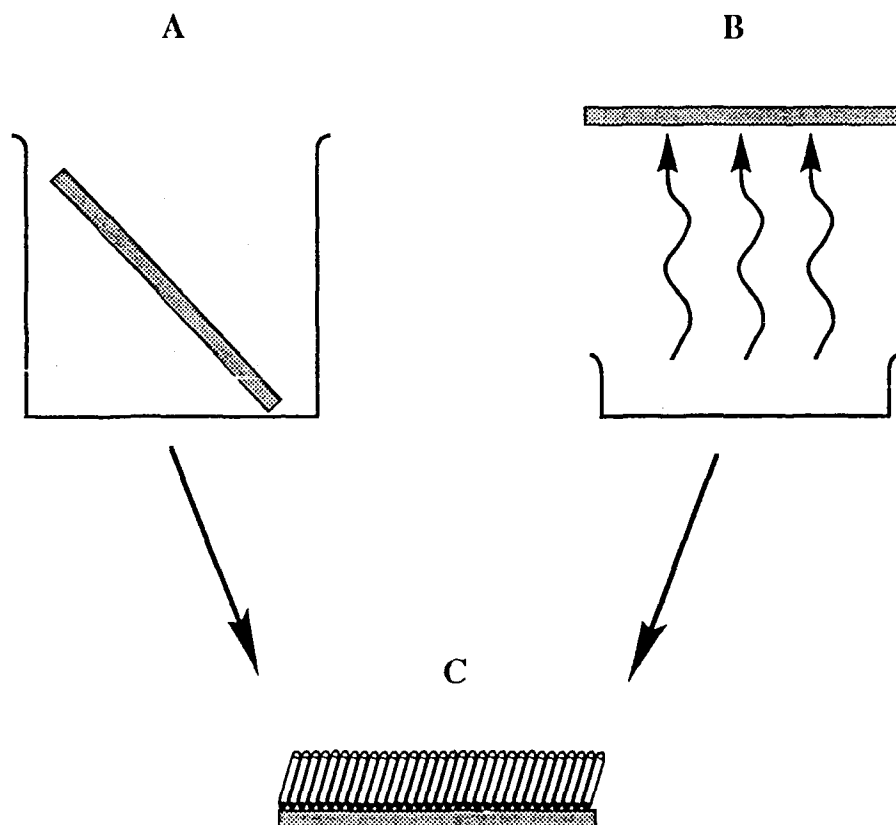


Figure 2. There are two approaches to forming self-assembled monolayers on gold. In scheme A, a gold film is immersed in a dilute solution of an alkanethiol; film formation is typically complete, as judged by macroscopic properties of the film, in one or two minutes. In scheme B, the gold film is exposed to an alkanethiol in the gas phase, either in air or under vacuum conditions. Both methods of preparation result in crystalline films with a cant angle of 30° , C. Film formation is driven by the strong, specific interaction of the thiol with the gold substrate.

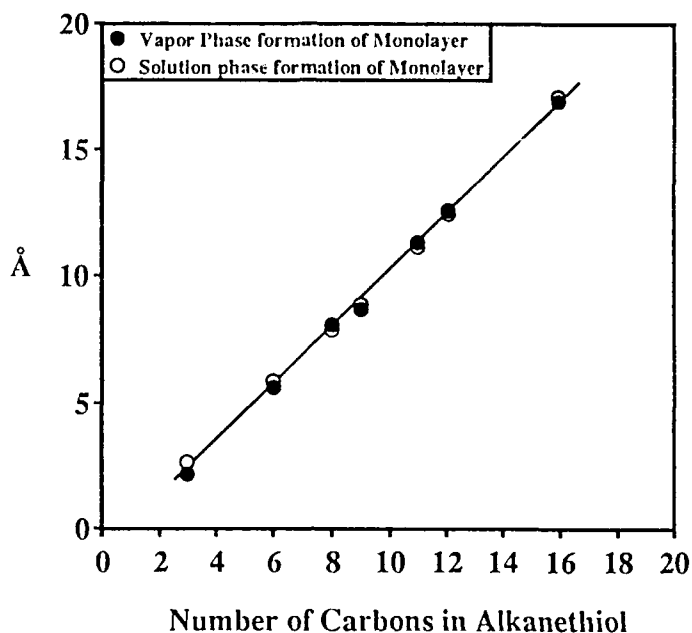


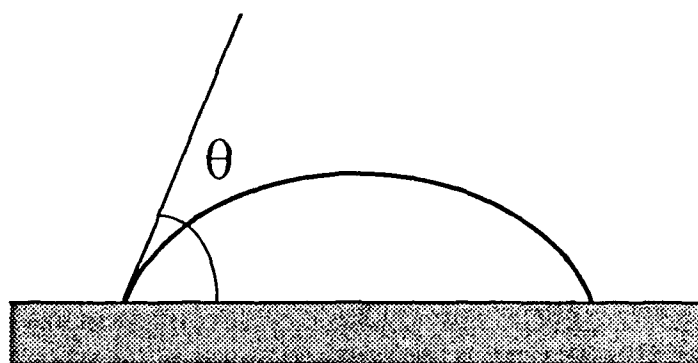
Figure 3. The thickness of the film on gold is easily controlled by changing the length of the alkanethiol. The average thickness of the film in angstroms, derived from the measurement of the intensity of the photoelectron signal of gold using an X-ray photoelectron spectrophotometer (XPS), is plotted as a function of total number of carbons in the alkanethiol. Films were made either by exposing the substrate to a vapor of the alkanethiol in air (black dots) or to a solution of the alkanethiol in ethanol (white dots). The line represents the best fit of the two sets of data; the slope of this line shows that the thickness of the film changes by approximately an angstrom per carbon in the alkanethiol. Techniques used to infer the thickness of a monolayer from the photoelectron intensity measured by XPS are given in C.D. Bain and G.M. Whitesides, *J. Phys. Chem*, 1989, 93, 1670.

their energy. The resulting systems can be shown to be monolayers having (at least locally) well-defined crystalline order.⁶

The advantages of this preparative technique (relative to Langmuir-Blodgett procedures or to the functionalization of pre-existing solids) from the vantage of organic surface chemistry are many. The monolayers are under thermodynamic control, and the order that they exhibit represents a minimum in energy. They are relatively free of defects. They will form on any appropriately exposed surface, even on the insides of objects and on very rough or porous surfaces. Assembly is easy -- the gold surface is simply exposed to the thiol for one or two hours at room temperature, removed, and washed. Most importantly, molecular self-assembly provides great control over certain of the physical properties of the monolayers. In particular, the thickness of the monolayer can be controlled in approximately one-angstrom steps by varying the length of the polymethylene chains (Figure 3), and the structure of the solid-liquid interface can be controlled by varying the terminal group X.

Only some of the rules for building well-ordered monolayers are presently known. In particular, the question of the influence of incommensurate sizes of the thiolate head groups and the tail group X on the structure of the monolayer is not well understood, and almost all studies have used thiols of the structure $\text{HS}(\text{CH}_2)_n\text{X}$. Nonetheless, for relatively small organic functional groups ($\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}, \text{CN}, \text{CO}_2\text{H}, \text{CONH}_2$, etc.) these monolayers constitute readily available systems that present sheets of organic functionality to liquid water. By working with an extended range of thiols $\text{HSRX}(\text{Y}, \text{Z}, \dots)$, both as pure compounds and as mixtures, we believe that it will eventually be possible to make a very broad range of surfaces.

Wetting and Contact Angle. We have explored the interaction between solid and liquid by measuring contact angles (Figure 4). This technique has three great advantages: First, it is experimentally very straightforward (at least for static drops). Second, it is very sensitive to the structure and composition of the outermost part of the surface. We will show below that the water "senses" the solid to a depth less than 10 \AA , and probably less than 5 \AA -- a depth sensitivity greater than that of many of the much more complex techniques of vacuum physics. Third, it is applicable to the



$$\gamma_{LV}\cos(\theta) = \gamma_{SV} - \gamma_{SL}$$

Figure 4. The figure shows the equilibrium shape of a drop of a liquid on a flat, solid surface. The contact angle of the liquid is the angle between the surface and the line drawn tangent to the sphere of liquid where the liquid meets the surface. Young's equation describes the relationship between the contact angle of the liquid and the surface tensions between each of the three phases (solid, liquid, and gas), where γ_{SL} , γ_{SV} , and γ_{LV} are the solid-liquid, solid-vapor, and liquid-vapor surface tensions.

exploration of solid-liquid interfaces and is not restricted to solid-vapor (vacuum) interfaces. It suffers from two corresponding disadvantages. It is a macroscopic rather than a molecular technique -- that is, it measures a property determined by the collective behavior of a large number of molecules (10^{12} - 10^{13} organic functional groups occupy the interface between solid and liquid for a drop of volume $1\ \mu\text{L}$). It also measures a ratio of surface energies rather than any single energy. In practice, the liquid-vapor interfacial free

$$\cos \theta = (\gamma_{SV} - \gamma_{SL})/\gamma_{LV}$$

energy (that is, the surface tension) is well known, so that the property measured directly is the difference between the solid-vapor and solid-liquid free energies. Varying the properties of the contacting liquid -- for example the size of its constituent molecules or its hydrophilicity -- can provide some insight into the nature of the forces due to the solid.

Single-Component Monolayers -- The Depth Sensitivity of Wetting. We have used monolayers comprising a single component to investigate a number of phenomena. One of relevance to molecular recognition is the depth sensitivity of wetting. How far into a solid does a liquid "see"?

Two experiments illustrate the approach that we have used in studying this question. In one, we prepared monolayers of a series of thiols $\text{HS}(\text{CH}_2)_{11}\text{O}(\text{CH}_2)_n\text{CH}_3$ in which a polar oxygen functionality was positioned at a controlled (by n) distance from the solid-liquid interface, and examined the wettability of these monolayers as a function of the carbon number n . We found that⁷ the influence of the length of the chain became constant for $n > \sim 6$ (Figure 5). That is, for $n > 6$, the wettability of the ether-containing monolayer surface was the same as the wettability of a pure hydrocarbon monolayer (such as that from $\text{HS}(\text{CH}_2)_{17}\text{CH}_3$). We conclude that the liquid water was able to sense the "buried" ether oxygen (by whatever mechanism -- dipole-dipole interaction through the superficial alkyl groups or penetration of water into the monolayer) only through less than $5\text{-}10\ \text{\AA}$ of alkane.

In the second experiment, we examined the wettability of monolayers of simple alkyl thiols $\text{HS}(\text{CH}_2)_n\text{CH}_3$ on gold. We found⁵ that the wettability of these monolayers also began to increase for $n < 10$ (Figure 6). Again, the

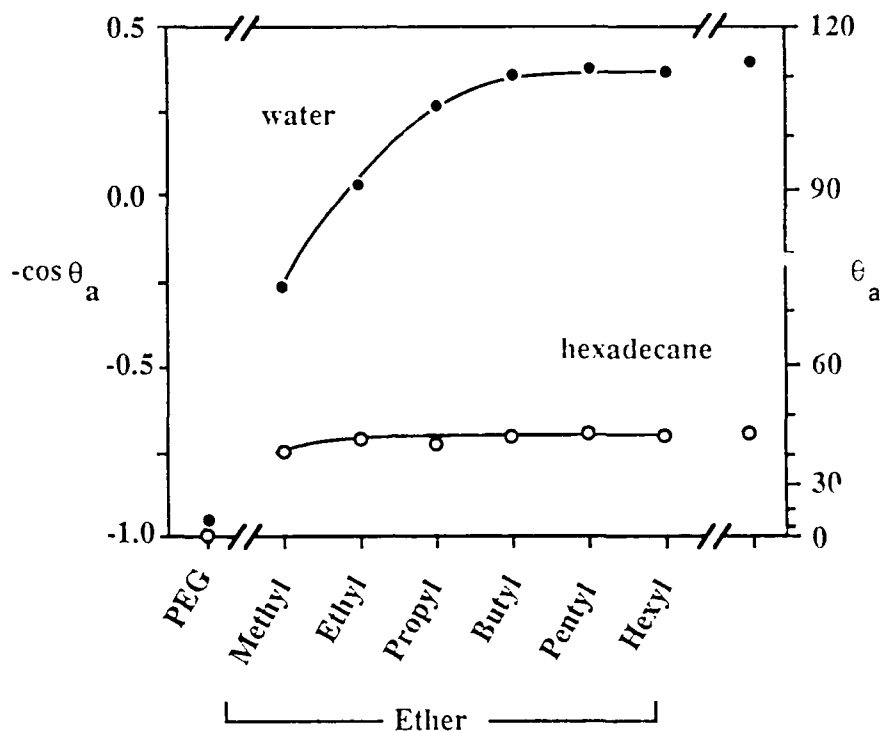


Figure 5. Films on gold formed from ω -mercaptoethers, $\text{HS}(\text{CH}_2)_{16}\text{O}(\text{CH}_2)_n\text{CH}_3$, have interfacial properties that change as the polar ether group is buried underneath the interface. The advancing contact angles of water and hexadecane are plotted as a function of n , the number of methylenes between the ether and the interface. Also shown are the contact angles on polyethylene glycol (PEG) and on a monolayer of docosanethiol on gold. The former surface is one in which the ether groups are fully exposed to the contacting liquid; the latter is one in which there is no contribution of an ether to the interfacial properties of the surface.

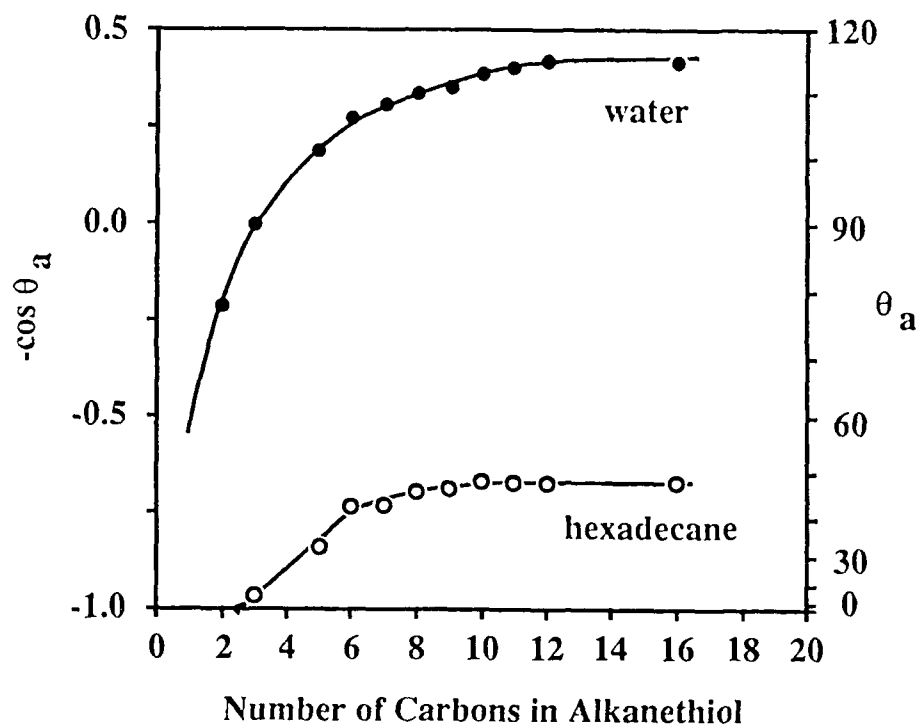


Figure 6. The contact angles on monolayers on gold formed from alkanethiols show progressively less dependence on the underlying gold substrate as the length of the alkanethiol increases. The advancing contact angles of water and hexadecane are plotted as a function of the number of carbons in the alkanethiol. The line through the data is included as a guide for the eye.

experiment does not distinguish between dipole-induced dipole interactions involving the water and the highly polarizable gold substrate from interactions resulting from penetration of water between the alkyl chains down to the gold. In either event, these experiments confirm the conclusion that wetting is a short-range interaction. In terms relevant to molecular recognition, the interaction of water with a protein or ligand is dominated by the structure of the outermost few angstroms of these molecules.

Related experiments involving functional groups positioned at the surface of polyethylene provide independent confirmation and illustration of the short-range character of wetting.⁸

Mixed Monolayers. Our most useful experimental systems are those based on monolayers incorporating two different components, $\text{HS}(\text{CH}_2)_m\text{X}$ and $\text{HS}(\text{CH}_2)_n\text{Y}$. By varying X and Y for chains of the same length ($m = n$), one can investigate interactions between X and Y.⁹ By making the chains of different lengths ($m \neq n$), one can introduce controlled amounts of disorder into the outermost parts of the monolayer.^{10,11}

One type of experiment based on mixed monolayers is particularly relevant to molecular recognition. We prepared monolayers containing a mixture of *n*-alkyl thiols having two different lengths, and examined the wetting of this system by liquid alkanes. The question of interest concerned intercalation -- was there any tendency for particular sizes or shapes of alkane molecules to interact particularly favorably with these disordered monolayers -- to "complete" the monolayer or to fill it to a dense, crystalline state? This type of shape-selective interaction would, of course, constitute a form of molecular recognition.

In brief, for this system (Figure 7), we found no evidence for this type of shape-selective wetting. This conclusion is not surprising, since all indications are that shape selectivity requires the presence of molecular cavities having defined size and rigid shape. There is no reason to expect such rigidity and order in a layer made up of loosely disordered, flexible, alkyl chains.

The experiment does, however, point to one future direction for self-assembled monolayers: that is, toward the development of techniques capable of assembling rigid components into monolayers. The ability to accomplish

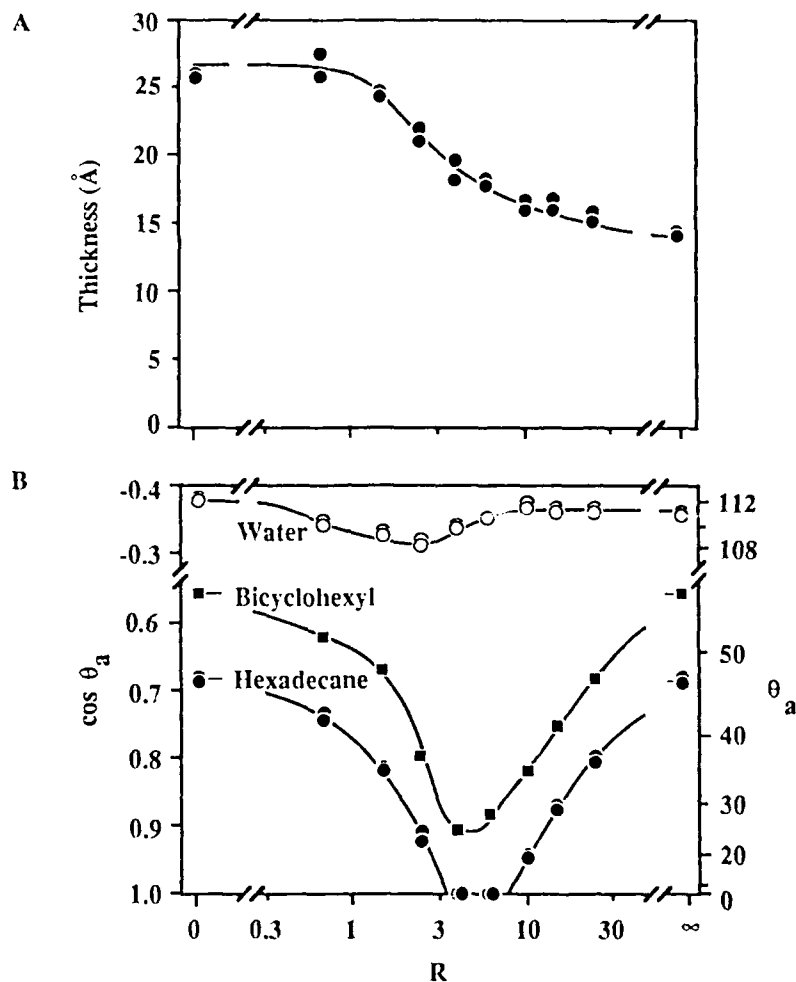


Figure 7. Mixed monolayers on gold formed from solutions containing mixtures of $\text{HS}(\text{CH}_2)_{21}\text{CH}_3$ and $\text{HS}(\text{CH}_2)_{11}\text{CH}_3$. The abscissa is the ratio, R , of the concentrations of $\text{HS}(\text{CH}_2)_{21}\text{CH}_3$ to $\text{HS}(\text{CH}_2)_{11}\text{CH}_3$ in solutions of ethanol. The upper graph plots the ellipsometric thickness of the monolayers. The lower graph plots the advancing contact angles of water, hexadecane, and bicyclohexyl. The line through the data is included as a guide for the eye.

this type of assembly would provide the basis for building surfaces having shape-selective cavities.

The Future: Does Wetting Really Have Anything to Offer Molecular Recognition?

Understanding wetting will certainly help in understanding solvation of proteins and ligands by water, and perhaps in understanding protein-ligand binding. Whether the field of molecular recognition persists for some time in its present mode -- using qualitative physical-organic models for important phenomena -- or whether it moves to a new mode based on (more) successful quantitative methods for computation and simulation remains to be seen. If the former, results from studies of wetting will become a part of the complex process of analog reasoning, pattern recognition, and intuition used now by medicinal and biological chemists in the design of new binding agents. If the latter, wetting will provide data from well-defined surfaces with which to test theories of solvation and potential functions for simulations.¹² Both connections between surface chemistry and wetting and recognition are conceptually indirect. Are more direct connections possible? I believe the answer to this question to be "yes," and propose the following topics as areas in which the fields will probably grow closer together.

1) Structurally Complex Surfaces. A protein can be considered, to one approximation, as a large scaffold used to construct a cavity of molecular dimensions.¹³ This view of a protein as a rigid entity is probably largely correct in some cases (i.e., immunoglobins) and incorrect in others. In any event, the surface supporting a self-assembled monolayer would, in principle, also serve admirably the function of scaffold. At present, we do not know how to assemble the cavity, but we understand the principles: Use multiple rigid components in making up the monolayer that will crystallize on the support into a thermodynamically stable, mixed, two-dimensional crystal with surface roughness appropriate to bind molecules.

At a more primitive level, one of the most versatile approaches to recognition employs partition chromatography to detect differences in recognition.¹⁴ The principles of self-assembly are exceptionally well suited to the rational design of sophisticated solid phases to test theories of adsorption, and, hence, of molecular recognition.

2) Ultra-Thin Liquid Films. It is clear for many liquids that proximity of the liquid to a solid support modifies the structure and properties of the liquid.¹⁵ For water, one, but not the only, manifestation of this interaction is the hydrophobic effect. Self-assembled monolayers provide the opportunity for studying the interaction between organic surfaces bearing complex organic functionality and water. These studies may be carried out either using wetting or through vapor adsorption and temperature-programmed desorption.

3) Studies Using the Force Balance. The force balance, an instrument developed by Tabor and Israelachvili,¹⁶ provides remarkably detailed information about the interactions between surfaces at distances of nanometers. All that is required to meld the types of studies described here using self-assembled monolayers with more quantitative studies using the force balance or, perhaps, ultimately, the atomic force microscope,¹⁷ is the development of routine procedures for preparing suitably flat substrates.

4) Models of Cell Surfaces. Much of practical importance involving molecular recognition takes place at the surface of cells.¹⁸ It is unclear how important the proximity of the receptor to the surface might be, or how surface attachment might be manifest. It is probable that many interesting aspects of receptor-ligand interactions in vivo will depend on the restriction of the receptor to a fluid, quasi-two-dimensional plane. Two contrasting examples of effects expected to be important are steric inhibition to binding of large ligands to receptors, due to proximity to the cell surface (and to the other components on it) and enhancement of binding of low-affinity systems (e.g. viral cell-surface receptors) due to a form of multi-point, cooperative attachment attributable to clustering of ligands by diffusion on the cell and clustering of ligands by structure on the virus.

Overall, we are convinced that much of molecular recognition is due to interaction between molecular surfaces (or more properly, interfaces), and that the study of model organic surfaces and interfaces will ultimately provide information of great value in understanding and controlling molecular recognition.

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